PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12562600/EJH/HPM/DYS	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT**/AU2005/000120	International filing date *(day/month/year)* 1 February 2005	Priority date *(day/month/year)* 3 February 2004

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

A61K 31/4178 (2006.01) ***A61K 33/24*** (2006.01) ***A61P 3/04*** (2006.01) ***A61K 33/00*** (2006.01)
A61P 1/14 (2006.01)

Applicant

AGT BIOSCIENCES LIMITED et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      [X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2 December 2005	05 May 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **JENNIFER FERNANCE** Telephone No. (02) 6283 2269

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2005/000120

Box No. I Basis of the report

1. With regard to the **language,** this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-62** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **63-69** received by this Authority on **21 April 2006** with the letter of **21 April 2006**
pages* received by this Authority on with the letter of

[ ] the drawings:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☐ claims Nos:

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. **18-31**
are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*

☒ no international search report has been established for said claim Nos. **18-31**

☐ A meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ Furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ Furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ Pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ A meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-17, 32-35	**YES**
	Claims	-	**NO**
Inventive step (IS)	Claims	-	**YES**
	Claims	1-17, 32-35	**NO**
Industrial applicability (IA)	Claims	1-17, 32-35	**YES**
	Claims	-	**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: Ahern
D2: Montell et al
D3: BIOMOL
D4: Sigma Catalogue
D5: Gomez et al

Novelty (N) Claims 1-17, 32-35

Claims 1-17 and 32-35 meet the criteria set forth in PCT Article 33(2) for novelty. The prior art published before the priority date does not disclose the use of ligands to the defined receptors to modulate the feeling of satiety. Therefore the subject matter of these claims is new and meets the requirements of Article 33(2) PCT with regard to novelty.

Inventive Step (IS) Claims 1-17 and 32-35

D1 discloses agents that are TRPV1 ligands and their activity in the modulation of satiety. D5 discloses that CB1 receptor agonists and antagonists modify satiety through the activity of TRPV1. TRPV-1 is a member of the TRPV group of cation channels. Thus the Person Skilled in the Art (PSA) would investigate the inhibition of related TRPV cation channels (such as TRPV2) and be led to the invention as presently claimed. Such an investigation would include the use of available blockers, promoters, agonists and antagonists of the receptors and/or direct modification of their genes. The PSA would also investigate the role of other TRPV channels in the role of satiety including gastric distension. Thus the PSA would be led to the invention as presently defined in claims 1-17 and 32-35 in light of D1 or D5.

D2 discloses the members of the TRP channel family including those presently claimed. Therefore D3 in combination with D1 or D5 deprive claims 1-17 and 32-35 of inventive step.

D3 and D4 disclose the commercially available SKF 96365 as a calcium ion channel modulator. Therefore D3 or D4 in combination with D1 or D5 deprive the claims 1-17 and 32-35 of inventive step.

(Continued in Supplemental Box)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims are not limited to selective agonists or antagonists of the defined mechanoreceptors. The limitation that the agent be directed towards TRPV2 is not seen as a true limitation in that the exemplified ruthenium red is also a known TRPV1 antagonist while SK&F 96365 has not been demonstrated to be a selective TRPV2 antagonist. As TRPV1 is also known to influence satiety (see novelty citations), the selectivity of SK&F 96365 for TRPV2 should be fully supported. The discovery that TRPV2 is involved in gastric distension may be of interest but does not confer novelty or inventiveness on known treatments.

Therefore, the claims are not fully supported by the description. There is no support for :

- the use of <u>any</u> agent that is a selective agonist/antagonist for each or any of the defined mechanoreceptors (the exemplified agents are not selective);
- the use of <u>any</u> agent that is an agonist/antagonist of the defined receptors which are not ligands for the TRPV1 receptors; or
- the use of <u>any</u> agent that inhibits or enhances the expression of the defined genes.

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [ ] in electronic form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [ ] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purposes of search and/or examination

   [ ] received by this Authority as an amendment* on

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of Box V:

The common general knowledge of the art is that gastric distension contributes to feelings of satiety and the PSA would appreciate that agents that affect gastric distension would be useful in the treatment of conditions that involve unusual appetites, for example, obesity. The specification at pages 47 and 48 describes known mechanoreceptors known to be involved in gastric distension. Therefore the PSA would investigate the role of ligands to these receptors in the modulation of satiety and be led to the invention as presently defined in claims 1-17 and 32-35. Therefore the subject matter of these claims is obvious and does not meet the requirements of Article 33(3) PCT with regard to inventive step.

Industrial Applicability (IA) Claims 1-17 and 32-35

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

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CLAIMS

1. A method for modulating the perception of satiety in a subject, said method comprising administering to said subject an effective amount of an agent selected from the list consisting of:

(i) an agent which is an agonist of a mechanoreceptor selected from the list consisting of ENAC, βENAC, γENAC, ACCN3, ACCN4, ASIC1, ASIC2, ASIC3, ASIC4, BLINAC/hiNaC (ACCN5), TREK1, TREK2, TRAAK (KCNK4), SCNN1C, KCNK2, TRPM1, TRPM2, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPC1, TRPC2, TRPC3, TRPC4, TRPC6, TRPV2, TRPV3, TRPV6 and TRPM8;

(ii) an agent which is an antagonist of a mechanoreceptor list in (i);

(iii) an agent which inhibits expression of a gene encoding a mechanoreceptor listed in (i); and

(iv) an agent which enhances expression of a gene encoding a mechanoreceptor listed in (i);

wherein increasing or decreasing the level of or activity of the mechanoreceptors changes the perception of satiety in said subject.

2. The method of Claim 1 wherein the mechanoreceptors are selected from the list consisting of TRPV2, ACCN5, TRPM1, TRPM4, TRPV6 and TRPV4.

3. The method of Claim 2 wherein the mechanoreceptor is TRPV2.

4. The method of Claim 1 or 2 or 3 wherein the agent is an agonist of the mechanoreceptor which promotes the perception of satiety.

5. The method of Claim 1 or 2 or 3 wherein the agent is an antagonist of the mechanoreceptor which reduces the perception of satiety.

6. The method of Claim 1 wherein the subject is a mammal.

7. The method of Claim 6 wherein the mammal is a primate.

8. The method of Claim 7 wherein the mammal is a human.

9. The method of Claim 6 wherein the mammal is a laboratory test animal.

10. The method of Claim 5 wherein the agent is an antagonist of TRPV2 selected from the list consisting of 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, ruthenium red dye and salts, homologs, orthologs, analogs, isomers, enantiomers, derivatives and functional equivalents thereof.

11. The method of Claim 10 wherein the agent is a ruthenium red dye selected from the list consisting of ruthenium (6t), tetradecaaminedi-m-oxotrihexachloride or a trans (8Cl) isomer or an enantiomer thereof, and an ammoniated ruthenium oxychloride or a steroisomer or enantiomer thereof.

12. A pharmaceutical composition when used to modulate the perception of satiety in a subject comprising an agent selected from the list consisting of:

(i) an agent which is an agonist of a mechanoreceptor selected from the list consisting of ENAC, βENAC, γENAC, ACCN3, ACCN4, ASIC1, ASIC2, ASIC3, ASIC4, BLINAC/hiNaC (ACCN5), TREK1, TREK2, TRAAK (KCNK4), SCNN1C, KCNK2, TRPM1, TRPM2, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPC1, TRPC2, TRPC3, TRPC4, TRPC6, TRPV2, TRPV3, TRPV6 and TRPM8;

(ii) an agent which is an antagonist of a mechanoreceptor list in (i);

(iii) an agent which inhibits expression of a gene encoding a mechanoreceptor listed in (i); and

(iv) an agent enhance expression of a gene encoding a mechanoreceptor listed in (i);

and one or more pharmaceutically acceptable carriers and/or diluents.

13. The pharmaceutical composition of Claim 12 wherein the agent is an antagonist of TRPV2 selected from the list consisting of 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, ruthenium red dye and salts, homologs, orthologs, analogs, isomers, enantiomers, derivatives and functional equivalents thereof.

14. The pharmaceutical composition of Claim 12 wherein the agent is a ruthenium red dye selected from the list consisting of ruthenium (6t), tetradecaaminedi-m-oxotrihexachloride or a trans (8Cl) isomer or an enantiomer thereof, and an ammoniated ruthenium oxychloride or a steroisomer or enantiomer thereof.

15. Use of an agent selected from the list consisting of:

(i) an agent which is an agonist of a mechanoreceptor selected from the list consisting of ENAC, βENAC, γENAC, ACCN3, ACCN4, ASIC1, ASIC2, ASIC3, ASIC4, BLINAC/hiNaC (ACCN5), TREK1, TREK2, TRAAK (KCNK4), SCNN1C, KCNK2, TRPM1, TRPM2, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPC1, TRPC2, TRPC3, TRPC4, TRPC6, TRPV2, TRPV3, TRPV6 and TRPM8;

(ii) an agent which is an antagonist of a mechanoreceptor list in (i);

(iii) an agent which inhibits expression of a gene encoding a mechanoreceptor listed in (i); and

(iv) an agent enhance expression of a gene encoding a mechanoreceptor listed in (i);

in the manufacture of a medicament for the control of obesity.

16. Use of Claim 15 wherein the agent is an antagonist of TRPV2 selected from the list consisting of 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, ruthenium red dye and salts, homologs, orthologs, analogs, isomers, enantiomers, derivatives and functional equivalents thereof.

17. Use of Claim 15 wherein the agent is a ruthenium red dye selected from the list consisting of ruthenium (6t), tetradecaaminedi-m-oxotrihexachloride or a trans (8Cl) isomer or an enantiomer thereof, and an ammoniated ruthenium oxychloride or a steroisomer or enantiomer thereof.

18. A method for treating or preventing symptoms of obesity, anorexia, need of satiation, weight maintenance conditions, metabolic energy levels and/or inflammatory disease conditions in an animal said method comprising administering to said animal an effective amount of a compound selected from a calcium uptake inhibitor or promoter, a blocker or promoter of TRPV2 calcium channels and a biological dye which inhibits or promotes calcium uptake for a time and under conditions to ameliorate one or more symptoms.

19. The method of Claim 18 wherein the compound is selected from 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, a ruthenium red dye and salt, homolog, ortholog, analog, isomer, enantiomer, derivative or functional equivalent thereof.

20. The method of Claim 19 wherein the compound is 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole and a ruthenium red dye or a salt or isomer or enantiomer thereof.

21. The method of Claim 19 wherein the compound is a ruthenium red dye or a salt or isomer or enantiomer thereof.

22. The method of Claim 18 or 19 or 20 or 21 wherein the animal is a mammal.

23. The method of Claim 22 wherein the mammal is a human.

24. The method of Claim 18 wherein the compounds modulate calcium ion uptake in cells of the stomach wall.

25. The method of Claim 24 wherein the cells are neuronal cells of the myenteric plexus.

26. Use of a compound selected from a blocker or promoter of TRPV2 calcium channels, a biological dye which inhibits or promotes calcium uptake of salts, homologs, orthologs, analogs, isomers, derivatives or functional equivalents thereof to modulate *inter alia* obesity, anorexia, satiation, weight maintenance, metabolic energy levels and/or inflammatory disease conditions in a subject in the manufacture of a medicament for the treatment of symptoms associated with obesity, anorexia, need for satiation, metabolic energy levels and/or inflammatory disease conditions.

27. Use of Claim 26 the compound is selected from 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole a ruthenium red dye and salt, homolog, ortholog, analog, isomer, enantiomer,derivative or functional equivalent thereof.

28. Use of Claim 27 wherein the compound is 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole and a ruthenium red dye or a salt or isomer or enantiomer thereof.

29. Use of Claim 27 wherein the compound is a ruthenium red dye or a salt or isomer enantiomer thereof.

30. Use of Claim 26 wherein the disease is obesity itself or various manifestations such as diabetes and disorders associated with imbalances in metabolic energy levels are disease and disorders associated with genetic disorders.

31. The method of Claim 18 or use of Claim 26 wherein the inflammatory condition is acne, angina, arthritis, aspiration pneumonia, empyema, gastroenteritis, inflammation, intestinal flu, necrotizing enterocolitis, pelvic inflammatory disease, pharyngitis, pleurisy, raw throat, rubor, sore throat, stomach flu and urinary tract infections, Chronic Inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Chronic Inflammatory Demyelinating Polyneuropathy and Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

32. A pharmaceutical composition when used for treating or controlling obesity, anorexia, satiation, weight maintenance, metabolic energy levels and inflammatory conditions comprising a compound selected from a calcium uptake inhibitor or promoter, a blocker or promoter of TRPV2 calcium channels and a biological dye which inhibits or promotes calcium uptake for a time and under conditions to ameliorate one or more symptoms and one or more pharmaceutically acceptable carriers and/or diluents.

33. The pharmaceutical composition of Claim 32 wherein the compound is selected from 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole a ruthenium red dye and salt, homolog, ortholog, analog, isomer, enantiomer, derivative or functional equivalent thereof.

34. The pharmaceutical composition of Claim 33 wherein the compound is 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole and a ruthenium red dye or a salt or isomer or enantiomer thereof.

35. The pharmaceutical composition of Claim 34 wherein the compound is a ruthenium red dye or a salt or isomer or enantiomer thereof.